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Reactions of hydroxylated sodium nitronates with acetic anhydride/pyridine

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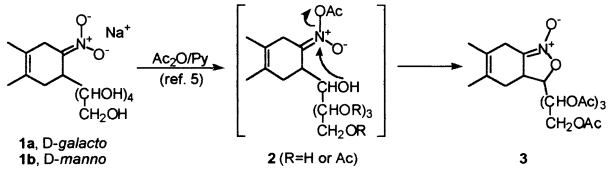
Abstract—Reactions with Ac_2O/Py of sodium nitronate salts derived from primary or secondary nitroalkanes bearing hydroxyl groups at γ or more remote positions have been studied. In all cases, the results could be explained through an acetic nitronic anhydride intermediate, whose evolution depends on conformational factors, and also on the type of the hydroxyl group. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Although alkyl nitronate anions can be considered as very important intermediates in synthetic organic chemistry, studies on some of their reactions still remain relatively lagged behind despite their extensive applications.[1] In particular, reports in which those compounds react with acid chlorides or anhydrides are scarce and rather old, most of the results being fragmentary and sometimes divergent.[2] The majority of explanations for these acylation processes have proposed the initial formation of a mixed carboxylic–nitronic acid anhydride;[2,3] however, this type of substances is generally very labile and only could be isolated (usually in poor yields) when metal salts of secondary nitroalkanes were used as the starting materials.[4]

In relation with the above cited reactions, we have described[5] that on treatment with Ac_2O/Py, the sodium salts of D-*galacto*- and D-*manno*-5-glyco-4-nitrocyclohexenes **1a** and **1b** led to highly stable chiral isoxazoline *N*-oxides **3** in excellent yields. Based on stereochemical arguments, we proposed a mechanism (Scheme 1) in which the not isolated acetic nitronic anhydride **2** could be the intermediate that cyclizes to give the final product.

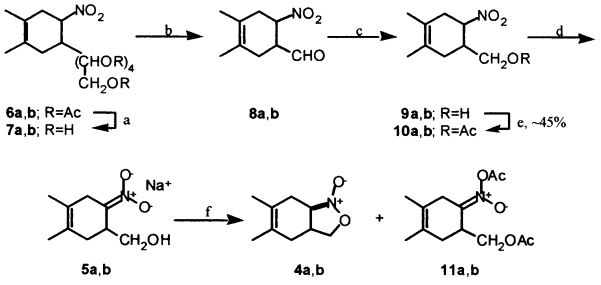


Scheme 1.

To further explore the details of this type of reaction, we have extended this method to include the use of other secondary or primary alkyl sodium nitronates, with the presence of γ-hydroxyl groups as requisite. Herein, a full account of our results is reported.

2. Results and discussion

First, with the aim to prepare the enantiomeric isoxazoline *N*-oxides **4a** and **4b**, we carried out treatment with Ac_2O/Py of hydroxymethylene cyclohexene nitronates **5a** and **5b**. As



Step	Parent compound (Configuration)	Product (Configuration)	Yield (%)
a	**6a** (D-*galacto*; 4*S*,5*S*)	**7a** (D-*galacto*; 4*S*,5*S*)	Quantitative
a	**6b** (D-*manno*; 4*R*,5*R*)	**7b** (D-*manno*; 4*R*,5*R*)	Quantitative
b	**7a** (D-*galacto*; 4*S*,5*S*)	**8a** (4*S*,5*S*)	80
b	**7b** (D-*manno*; 4*R*,5*R*)	**8b** (4*R*,5*R*)	98
c	**8a** (4*S*,5*S*)	**9a** (4*S*,5*S*)	85
c	**8b** (4*R*,5*R*)	**9b** (4*R*,5*R*)	77
d	**9a** (4*S*,5*S*)	**5a** (5*S*)	Quantitative
d	**9b** (4*R*,5*R*)	**5b** (5*R*)	Quantitative
f	**5a** (5*S*)	**4a** (5*S*) and **11a** (5*S*)	10 and 13, respectively
f	**5b** (5*R*)	**4b** (5*R*) and **11b** (5*R*)	9 and 11, respectively

Scheme 2. (a) 4 M HCl/MeOH, reflux, 4 h; (b) $NaIO_4$, 1:2.3 MeOH/H_2O, 0°C, 15 min; (c) $NaBH_4$, MeOH, room temperature, 15 min; (d) 2 M NaOMe/MeOH, room temperature, 4 h; (e) 1:20 Ac_2O/Py, room temperature, 5 h; (f) 1:1 Ac_2O/Py, room temperature, 5 h.

Keywords: nitro compounds; nitronate salts; acetic nitronic anhydrides.

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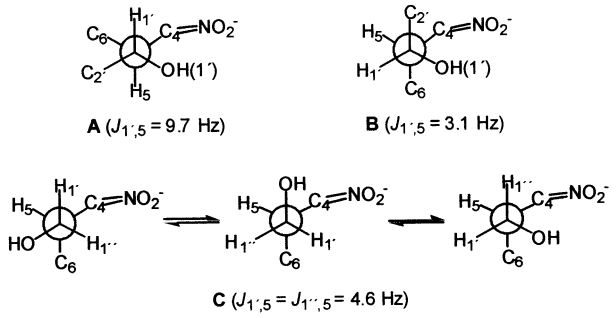


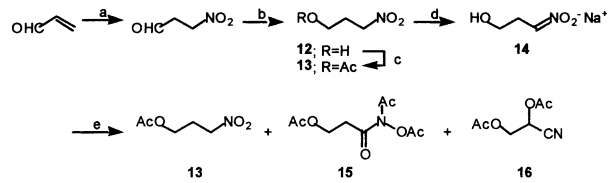
Figure 1. Newman projections along the C1′–C5 bonds in nitronates **1a** (**A**), **1b** (**B**) and **5** (**C**).

shown in Scheme 2, these latter compounds were obtained from pentaacetylated *trans*-D-*galacto*- and D-*manno*-5-glyco-4-nitrocyclohexenes[6] **6a**,**b** through parallel processes involving: (a) acid-catalyzed deacetylation of their sugar side-chains, leading to **7a**,**b**;[6] (b) oxidative cleavage of these to give enantiomeric cyclohexene nitroaldehydes **8a**,**b**;[6] (c) sodium borohydride reduction of the carbonyl group to yield **9a**,**b**; and (d), treatment of these with sodium methoxide in methanol to produce the salts **5a**,**b**.

In contrast with what occurred from **1a**,**b**, the reaction of **5a**,**b** with Ac_2O/Py (Scheme 2, Step f) led to complex mixtures, from which isoxazoline *N*-oxides **4a**,**b** and acetic nitronic anhydrides **11a**,**b** were respectively isolated, as oils, by preparative thin layer chromatography.

Because of their enantiomeric relationship, each pair of compounds **4** and **11** showed spectral identity and nearly equal and opposite values for their optical rotations. The ^{1}H and ^{13}C NMR spectra of isoxazolines were very similar to those of their nitronate precursors; as expected, the most significant differences between chemical shifts of these two types of compounds were found in the methylene group that is involved in the cyclization; thus, signals for protons H-1′ and H-1″ (4.67 and 4.07 ppm) and carbon C-1′ (70.5 ppm) in **4** appear considerably deshielded when they are compared with the same in nitronates **5** (H-1′,1″ at 3.42 and 3.35 ppm; C-1′ at 61.6 ppm).

The acetic nitronic anhydrides **11** were obtained as greenish blue-colored oils, which showed no decomposition after several weeks of storage at room temperature in the dessicator. The NMR spectra of these compounds agree with their structures, thus appearing two distinct acetate groups and three olefinic carbons. Furthermore, the existence of geometrical isomers at the anhydride groups could be deduced, because duplication of the signals (approximate ratio 7:1) has been observed. However, we have not attempted to separate them and also not assigned the signals to their structures.



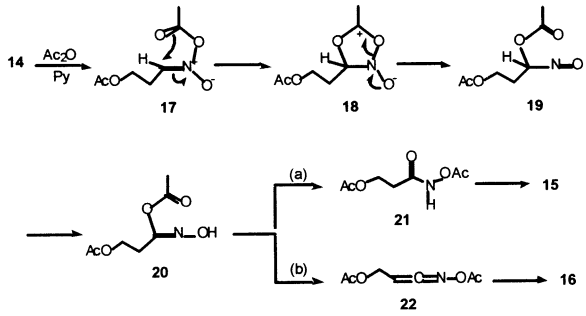
Scheme 3. (a) $NaNO_2$/HOAc, THF, 0°C, 4 h; (b) $NaBH_4$/MeOH, 0°C, 15 min; (c) 1:1 Ac_2O/Py, 0°C, 12 h; (d) 2 M NaOMe/MeOH, room temperature, 5 h; (e) 1:1 Ac_2O/Py, room temperature, 5 h.

We think that the different behavior between nitronates **1** and **5** against Ac_2O/Py may be explained by considering two circumstances: (i) the hydroxyl group involved in the cyclization is secondary in **1** and primary in **5**; hence acetylation of this group in the latter compound must be easier,[7] thus precluding, in part, the cyclization reaction leading to **4**; (ii) the coupling constants between H-1′ and H-5 in glyco-cyclohexene nitronates **1a** and **1b** (9.7 and 3.1 Hz, respectively) support conformations **A** and **B** (Fig. 1), in which the proximity between the hydroxyl group at C-1′ and the nitrogen should favor the cyclization. On the contrary, this reaction should be less favored in the case of nitronates **5**, because the intermediate values for $J_{1',5}$ and $J_{1'',5}$ in these compounds (both of 4.6 Hz) are suggesting a conformational mixture **C**, in which the relative average positions for the hydroxyl group and the nitrogen are more distant than in **A** or **B**.

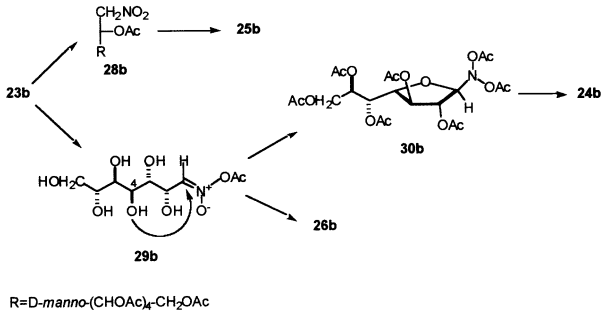
In order to extend the study of this reaction to the simplest system bearing nitro and hydroxyl functions in 1,3-relative positions, we have used 3-nitropropanol **12**[8] as starting material. As shown in Scheme 3, this compound has been obtained by addition of sodium nitrite to acrolein, followed by reduction of the resulting 3-nitropropanal with $NaBH_4$;[9] then, treatment of a methanolic solution of either **12**, or its acetate **13**, with an excess of sodium methoxide yielded quantitatively sodium nitronate **14** as a white solid.

The reaction of **14** with Ac_2O/Py proceeded in a different manner with what is described above from cyclohexene nitronates. In this case, there was no evidence of the formation of either hypothetical acetic nitronic anhydride or isoxazoline-*N*-oxide;[10] instead, ^{1}H NMR examination of the crude mixture product showed that it contained, almost exclusively, compounds **13**, **15** and **16** in relative ratio 1.6:2.2:1, respectively. By preparative thin layer chromatography of this mixture, we could isolate a pure analytical sample of hydroxamic acid derivative **15**,[11] but no complete separation was achieved between 3-acetoxy-1-nitropropane **13** and 2,3-diacetoxypropanenitrile **16**.[12] The ^{1}H and ^{13}C NMR spectra of **15** in deuteriochloroform showed the presence of three methyl and four carbonyl groups; at room temperature, methylenic carbon C-2 (35.5 ppm) and its protons H-2 and H-2′ (3.10 and 3.00 ppm) gave broad signals, probably due to restricted rotation of bonds C-1–C-2 and C-1–N. Concerning nitrile **16**, the H-2 proton appears as a triplet (5.58 ppm, J∼5.0 Hz), due to its couplings with H-3 (dd, 4.46 ppm) and H-3′ (dd, 4.35 ppm); resonances for C≡N, C-2 and C-3 carbons were found at 114.4, 59.1 and 60.6 ppm, respectively.

As shown in Scheme 4, we propose that formation of compounds **15** and **16** could occur with common intermediates at the first steps; thus, the initially formed mixed carboxylic–nitronic anhydride **17** would suffer a N→C acetate migration, probably through cyclic intermediate **18**, affording a nitrosoderivative **19**, which tautomerizes to oxime **20**; then, either (a) rearrangement or (b) 1,2-elimination of acetic acid would lead, respectively, to *O*-acyl



Scheme 4.



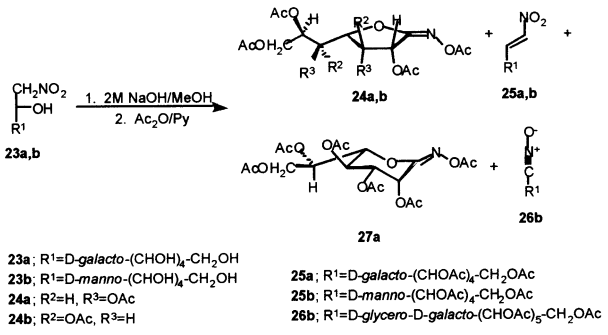
Scheme 6.

hydroxamic acid **21** and *O*-acyl ketene oxime **22**, from which the products **15** and **16** were originated.

Finally, we have also included in our study the previously described 1-deoxy-1-nitro-D-*glycero*-L-*manno* heptitol[13] **23a** and 1-deoxy-1-nitro-D-*glycero*-D-*galacto* heptitol[14] **23b**. Treatment of either of these both compounds with 2 M aqueous sodium hydroxyde, followed by reaction of the presumably formed sodium nitronates with acetic anhydride and pyridine (Scheme 5) afforded crude mixtures, which were analyzed by ^{1}H NMR spectroscopy. From the spectra, we observed that **23a** led to a mixture containing, almost exclusively, **24a**, **25a**[13] and **27a** in respective ratio 3.6:2.6:1.0. When starting from **23b**, the result was somewhat similar, and **24b**, **25b**[14] and **26b** (relative ratio 4.5:3.5:1.0), together with other minor unidentified products, were present in the resulting mixture.[15]

Structural assignment for the new compounds are supported by spectroscopic data (IR, NMR and HRMS) from pure samples, isolated by preparative thin layer chromatography. Thus, for both types of lactone oximes **24** and **27**, the H-2 protons were those encountered at the lowest field (doublets at ca. 5.9 ppm), due to their proximity with the carbon–nitrogen double bond. The ring-sizes were deduced from chemical shifts for H-4 or H-5, that revealed if their adjacent carbons had been acetylated; for 1,4-lactone oximes **24a**,**b** the signals for H-4 (dd at ca. 4.6 ppm) appeared at higher field than the other protons on secondary carbons (5.6–5.3 ppm), whereas the same is true for proton H-5 (dd at 4.30 ppm) in 1,5-lactone oxime **27a**. Furthermore, the presence of oxime carbons accorded with ^{13}C NMR resonances at ca. 155 ppm.

Besides the absence of signals for H-1, protons in the



23a; R^1=D-*galacto*-(CHOH)$_4$-CH$_2$OH
23b; R^1=D-*manno*-(CHOH)$_4$-CH$_2$OH
24a; R^2=H, R^3=OAc
24b; R^2=OAc, R^3=H
25a; R^1=D-*galacto*-(CHOAc)$_4$-CH$_2$OAc
25b; R^1=D-*manno*-(CHOAc)$_4$-CH$_2$OAc
26b; R^1=D-*glycero*-D-*galacto*-(CHOAc)$_5$-CH$_2$OAc

Scheme 5.

fragment C-2–C-7 of **26b** showed chemical shifts and coupling constants that were very similar to those described for acyclic peracetylated 1-deoxy-1-nitro heptitols with the same configurations;[16] also, an IR band at 2350 cm^{-1} (C≡N) and HRMS data are in agreement with the proposed nitrile oxide structure. As was found for other compounds of this type,[17] **26b** proved to be unstable and decomposition was observed, even at 0°C, after a few days of storage.

The above results can be explained by the processes shown in Scheme 6 for **23b**; thus, protonation of the intermediate salt and acetylation of the hydroxyl groups would lead, after elimination of acetic acid in **28b**, to 1-nitroalkene **25b**. On the other hand, nucleophilic attack of OH-4 on C-1 of acetic nitronic anhydride **29b** would give, through intermediate **30b**, the 1,4-lactone oxime **24b**.[18] The formation of nitrile oxide **26b** could be also explained from anhydride **29b**, by acetic acid elimination between the nitrogen atom and C-1.

Since coupling constants between protons on C-2–C-6 backbones of both **23a** and **23b** supported extended zig-zag planar conformations (as it is showed for **29b** in Scheme 6), we postulate that a nucleophilic substitution reaction between OH-3 and the nitrogen leading to an isoxazoline-*N*-oxide, would be unfavored. On the contrary, processes in which OH-4 (or OH-5) attack at C-1, or those in which cyclization does not occur, would be more feasible.

In conclusion, the foregoing new results complement previous studies[2,3] which were carried out for nitronates under acetylation reaction conditions, where is proposed a key mixed carboxylic–nitronic anhydride intermediate. In addition, the presence of hydroxyl groups at γ or more remote positions allows the possibility of intramolecular nucleophilic cyclizations, whose course is influenced by conformational effects and by the type of the involved hydroxyl group. Other substrates are under current investigation in order to extend the generality of and to improve the methodology.

3. Experimental

3.1. General

Solvents were evaporated under reduced pressure below 40°C bath temperature. Melting points were determined with an Electrothermal 8100 apparatus and are uncorrected. Optical rotations were obtained at 20±2°C with a

Perkin–Elmer 241 polarimeter. Infrared spectra were recorded in the range 4000–600 cm^{-1} with Perkin–Elmer 399 or Midac FT-IR spectrophotometers. NMR spectra were recorded at 20°C on a Bruker spectrometer AM 400 (400.13 MHz for ^1H, 100.62 MHz for ^{13}C) with TMS or residual $CHCl_3$/DMSO as internal standards. NMR assignments were confirmed by homonuclear double-resonance experiments, and DEPT. Mass spectra were recorded on a VG Autospec spectrometer. TLC was performed on precoated plates of Silica Gel-60 GF254 (Merck), with visualization of spots by UV light or iodine vapor, and the solvent systems specified. Preparative thin layer chromatography was carried out on 0.20 mm Merck Silica Gel-60 PF254 plates.

3.1.1. (4*S*,5*S*)-5-Hydroxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene (9a). To a stirred solution of (4*S*,5*S*)-5-formyl-1,2-dimethyl-4-nitrocyclohex-1-ene **8a**[6] (0.41 g, 2.26 mmol) in methanol (12 mL) was added $NaBH_4$ (0.09 g, 2.26 mmol). After stirring for 15 min at room temperature, the solution was diluted with water (12 mL) and extracted with methylene dichloride (4×25 mL); then, the extracts were washed with water (2×25 mL), dried ($MgSO_4$), and evaporated to yield 0.35 g (85%) of compound **9a** as a colorless oil: R_f 0.52 (3:1 hexane/ethyl acetate); $[\alpha]_D$=+68.3°, $[\alpha]_{578}$=+70.9°, $[\alpha]_{546}$=+78.5°, $[\alpha]_{436}$=+116.7° (*c* 0.46, $CHCl_3$); ν_{max} (film) (cm^{-1}) 3550 and 3400 (OH), 2980, 2910, 2870, 2840 (C–H), 1545, 1365 (NO_2), 1050, 1020 (C–O); ^1H NMR ($CDCl_3$) δ 4.72 (td, 1H, $J_{4,3a}\approx J_{4,5}$=10.1 Hz, $J_{4,3b}$=5.6 Hz, H-4), 3.64 (dt, 1H, $J_{1',1''}$=11.3 Hz, $J_{1',5}$=4.6 Hz, H-1′), 3.59 (dt, 1H, $J_{1'',5}$=4.6 Hz, H-1″), 2.73 (br dd, 1H, H-3a), 2.46 (dd, 1H, $J_{3a,3b}$=17.1 Hz, H-3b), 2.38 (m, 1H, H-5), 2.14 (m, 2H, H-6a, H-6b), 1.74 (t, 1H, $J_{1',OH}\approx J_{1'',OH}$=4.6 Hz, OH), 1.64 (s, 3H, Me), 1.63 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 124.8, 121.5 (C-1, C-2), 84.4 (C-4), 62.9 (C-1′), 39.8 (C-5), 35.7, 30.1 (C-3, C-6), 18.5 (Me-1, Me-2). CI MS *m/z* (rel. int.): 186 (M+H, 1), 168 (M−OH, 6), 138 (M−H−NO_2, 19), 121 (M−H−OH−NO_2, 28), 107 (M−OH−NO_2−CH_3, 100). HRMS (CI) calcd for $C_9H_{15}NO_3$+H: 186.1130. Found $(M+H)^+$ 186.1122.

3.1.2. (4*R*,5*R*)-5-Hydroxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene (9b). Following the same procedure above described for the preparation of its enantiomer **9a**, reduction of (4*R*,5*R*)-5-formyl-1,2-dimethyl-4-nitrocyclohex-1-ene **8b**[6] (0.49 g, 2.67 mmol) led to the title compound as a colorless oil (0.38 g, 77%): R_f 0.52 (3:1 hexane/ethyl acetate); $[\alpha]_D$=−67.5°, $[\alpha]_{578}$=−70.3°, $[\alpha]_{546}$=−78.6°, $[\alpha]_{436}$=−114.6° (*c* 0.47, $CHCl_3$); IR, ^1H and ^{13}C NMR data matched those for **9a**.

3.1.3. (4*S*,5*S*)-5-Acetoxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene (10a). To a stirred solution of (4*S*,5*S*)-5-hydroxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene **9a** (0.29 g, 1.57 mmol) in dry pyridine (3 mL) was added acetic anhydride (0.15 mL). After stirring for 5 h at room temperature, the solution was poured onto ice cold water, extracted with methylene dichloride (4×25 mL) and washed successively with 1 M hydrochloric acid (2×25 mL), saturated aqueous sodium hydrogencarbonate (2×25 mL) and water (2×25 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated, yielding the title compound as a colorless oil (0.15 g, 43%): R_f 0.68 (3:1 hexane/ethyl acetate); $[\alpha]_D$=+62.6°, $[\alpha]_{578}$=+64.0°, $[\alpha]_{546}$=+71.6°, $[\alpha]_{436}$=+110.0° (*c* 0.50, $CHCl_3$); ν_{max} (film) (cm^{-1}) 2960, 2910, 2870, 2850 (C–H), 1740 (C=O), 1540, 1365 (NO_2), 1220, 1040, 1020 (C–O); ^1H NMR ($CDCl_3$) δ 4.63 (td, 1H, $J_{4,3a}\approx J_{4,5}$=9.9 Hz, $J_{4,3b}$=5.3 Hz, H-4), 4.05 (dt, 2H, $J_{1',1''}$=11.6 Hz, $J_{1',5}\approx J_{1'',5}$=5.0 Hz, H-1′, H-1″), 2.72 (br d, 1H, H-3a), 2.64 (m, 1H, H-5), 2.49 (dd, 1H, $J_{3a,3b}$=16.6 Hz, H-3b), 2.18 (dd, 1H, $J_{6a,6b}$=18.7 Hz, $J_{5,6a}$=6.4 Hz, H-6a), 2.06 (br d, 1H, H-6b), 2.05 (s, 3H, OAc), 1.66 (s, 3H, Me), 1.63 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 170.7 (O*C*OCH$_3$), 124.3, 121.8 (C-1, C-2), 84.5 (C-4), 64.5 (C-1′), 36.7 (C-5), 35.8, 32.9 (C-3, C-6), 20.6 (OCO*C*H$_3$), 18.5 (Me-1, Me-2). CI MS *m/z* (rel. int.): 228 (M+H, 19), 197 (M−NO, 8), 181 (M−NO_2, 48), 168 (M−OAc, 13), 137 (M−NO−HOAc, 51), 121 (M−NO_2−HOAc, 100). HRMS (CI) calcd for $C_{11}H_{17}NO_4$+H: 228.1235. Found $(M+H)^+$ 228.1230.

3.1.4. (4*R*,5*R*)-5-Acetoxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene (10b). Following the same procedure above described for the preparation of its enantiomer **10a**, acetylation of (4*R*,5*R*)-5-hydroxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene **9b** (0.35 g, 1.89 mmol) led to the title compound as a colorless oil (0.20 g, 46%): R_f 0.68 (3:1 hexane/ethyl acetate); $[\alpha]_D$=−61.0°, $[\alpha]_{578}$=−62.3°, $[\alpha]_{546}$=−70.4°, $[\alpha]_{436}$=−107.9° (*c* 0.50, $CHCl_3$); IR, ^1H and ^{13}C NMR data matched those for **10a**.

3.1.5. Sodium salt of (4*S*,5*S*)-5-hydroxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene (5a). To a stirred solution of (4*S*,5*S*)-5-hydroxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene **9a** (0.36 g, 1.94 mmol) in methanol (5 mL) was added dropwise a solution of 2 M sodium methoxide in methanol (1.22 mL, 2.44 mmol). After stirring for 4 h at room temperature, evaporation of the solvent afforded **5a** as an amorphous hygroscopic solid, which was washed with cold acetone and filtered (0.40 g, quantitative): mp 144–146°C; $[\alpha]_D$=+22.2°, $[\alpha]_{578}$=+24.1° (*c* 0.58, H_2O); ν_{max} (KBr) (cm^{-1}) 3500–3200 (OH), 2928 (C–H), 1155, 1020 (C–O); ^1H NMR (D_2O) δ 3.42 (dd, 1H, $J_{1',1''}$=10.6 Hz, $J_{1',5}$=6.4 Hz, H-1′), 3.35 (dd, 1H, $J_{1'',5}$=8.7 Hz, H-1″), 3.24 (m, 1H, H-5), 2.93 (d, 1H, $J_{3a,3b}$=22.8 Hz, H-3a), 2.63 (d, 1H, H-3b), 2.19 (br d, 1H, H-6a), 2.02 (d, 1H, $J_{6a,6b}$=14.7 Hz, H-6b), 1.56 (s, 6H, Me-1, Me-2); ^{13}C NMR (D_2O) δ 127.3 (C-4), 123.9, 122.6 (C-1, C-2), 61.6 (C-1′), 37.6 (C-5), 32.4, 31.3 (C-3, C-6), 18.7, 18.0 (Me-1, Me-2).

3.1.6. Sodium salt of (4*R*,5*R*)-5-hydroxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene (5b). Following the same procedure above described for the preparation of its enantiomer **5a**, (4*R*,5*R*)-5-hydroxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene **9b** (0.50 g, 2.70 mmol) led to the title compound as an amorphous hygroscopic solid (0.56 g, quantitative): mp 144–146°C; $[\alpha]_D$=+21.1°, $[\alpha]_{578}$=+23.2° (*c* 0.57, H_2O); IR, ^1H and ^{13}C NMR data matched those for **5a**.

3.1.7. (3a*S*)-5,6-Dimethyl-(3,3a,4,7)-tetrahydrobenzisoxazoline *N*-oxide (4a) and 1,2-dimethyl-(5*S*)-5-acetoxymethyl-4-(*O*-acetyl-*aci*-nitro)-cyclohex-1-ene (11a). *Method A*. Following the same procedure above

described for the preparation of **10a**, treatment of the sodium salt of (4*S*,5*S*)-5-hydroxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene **5a** (0.92 g, 4.42 mmol) with pyridine (9 mL) and acetic anhydride (9 mL) led to a crude oily residue (0.68 g), which was submitted to preparative thin layer chromatography (1:1 hexane/ethyl acetate), thus affording analytically pure samples of the title compounds. *Data for **4a***. Colorless oil (0.075 g, 10%); R_f 0.46 (1:1 hexane/ethyl acetate); $[\alpha]_D$=+148.6°, $[\alpha]_{578}$=+156.4°, $[\alpha]_{546}$=+169.6° (*c* 0.28, $CHCl_3$); ν_{max} (film) (cm^{-1}) 2970, 2920, 2900, 2860 (C–H), 1700, 1650 (C=N), 1240, 1220 (C–O); ^1H NMR ($CDCl_3$) δ 4.67 (dd, 1H, $J_{1',5}$=9.3 Hz, H-1′), 4.07 (t, 1H, $J_{1'',5}\approx J_{1',1''}$=8.1 Hz, H-1″), 3.54 (m, 1H, H-5), 3.02 (d, 1H, $J_{3a,3b}$=21.5 Hz, H-3a), 2.90 (d, 1H, H-3b), 2.36 (dd, 1H, $J_{6a,6b}$=15.9 Hz, $J_{5,6a}$=7.0 Hz, H-6a), 2.21 (br dd, 1H, $J_{5,6b}$=11.7 Hz, H-6b), 1.73 (s, 3H, Me), 1.68 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 124.5, 122.3 (C-1, C-2), 115.6 (C-4), 70.5 (C-1′), 40.4 (C-5), 36.8, 29.1 (C-3, C-6), 19.2, 18.7 (Me-1, Me-2). HRMS (CI) calcd for $C_9H_{13}NO_2$: 167.0946. Found M^+ 167.0947. *Data for **11a***. Greenish blue-colored oil (0.155 g, 13%); R_f 0.43 (1:1 hexane/ethyl acetate); $[\alpha]_D$=+852.0°, $[\alpha]_{578}$=+790.0°, $[\alpha]_{546}$=+631.5°, $[\alpha]_{436}$=+481.1° (*c* 0.46, $CHCl_3$); ν_{max} (film) (cm^{-1}) 2915 (C–H), 1744 (C=N), 1225, 1042 (C–O); ^1H NMR ($CDCl_3$) δ 4.42 (dd, 1H, $J_{1',5}$=4.2 Hz, $J_{1',1''}$=11.2 Hz, H-1′), 3.93 (dd, 1H, $J_{1'',5}$=7.6 Hz, H-1″), 2.94 (d, 1H, $J_{3a,3b}$=18.2 Hz, H-3a), 2.62 (m, 1H, H-5), 2.33 (dd, 1H, $J_{5,6a}$=4.5 Hz, $J_{6a,6b}$=17.9 Hz, H-6a), 2.27 (br d, 1H, H-3b), 2.06 (dd, 1H, $J_{5,6b}$=9.9 Hz, H-6b), 1.74 (s, 3H, Me), 1.71 (s, 3H, Me); ^{13}C NMR ($CDCl_3$) δ 170.7, 168.4 (O*C*OCH$_3$), 123.8, 122.5, 122.0 (C-1, C-2, C-4), 62.1 (C-1′), 40.1 (C-5), 35.8, 32.4 (C-3, C-6), 21.1, 20.7 (OCO*C*H$_3$), 18.7, 18.5 (Me-1, Me-2); HRMS (CI) calcd for $C_{13}H_{19}NO_5$+H: 270.1341. Found $(M+H)^+$ 270.1354.

Method B. To a stirred solution of (4*S*,5*S*)-5-hydroxymethyl-1,2-dimethyl-4-nitrocyclohex-1-ene **9a** (0.10 g, 0.54 mmol) in methanol (2 mL) was added dropwise a solution of 2 M sodium methoxide in methanol (0.35 mL, 0.68 mmol). After stirring for 5 h at room temperature, removal of the solvent afforded 0.11 g of an amorphous solid, which was dissolved in dry pyridine (3 mL) and treated with acetic anhydride (3 mL) for 5 h; then, work-up of the reaction mixture as described for **10a**, yielded a crude oily residue (0.07 g) from which analytically pure samples of the title compounds could be isolated, by preparative thin layer chromatography (1:1 hexane/ethyl acetate).

3.1.8. (3a*R*)-5,6-Dimethyl-(3,3a,4,7)-tetrahydrobenzisoxazoline *N*-oxide (4b) and 1,2-dimethyl-(5*R*)-5-acetoxymethyl-4-(*O*-acetyl-*aci*-nitro)-cyclohex-1-ene (11b). Following the same procedure above described in *Method A* for the preparation of their enantiomers **4a** and **11a**, treatment of **5b** (0.50 g, 2.40 mmol) with pyridine (5 mL) and acetic anhydride (5 mL) led to an oily residue (0.38 g), from which the title compounds could be isolated, by preparative thin layer chromatography (1:1 hexane/ethyl acetate). *Data for **4b***. Colorless oil (0.037 g, 9%); R_f 0.46 (1:1 hexane/ethyl acetate); $[\alpha]_D$=−151.2°, $[\alpha]_{578}$=−159.7°, $[\alpha]_{546}$=−173.4° (*c* 0.30, $CHCl_3$). IR, ^1H and ^{13}C NMR data matched those for **4a**. *Data for **11b***. Greenish blue-colored oil (0.071 g, 11%); R_f 0.43 (1:1 hexane/ethyl acetate); $[\alpha]_D$=−842.0°, $[\alpha]_{578}$=−781.0°, $[\alpha]_{546}$=−626.4°, $[\alpha]_{436}$=−476.8° (*c* 0.40, $CHCl_3$). IR, ^1H and ^{13}C NMR data matched those for **11a**.

3.1.9. 3-Acetoxy-1-nitropropane (13). Following the same procedure above described for the preparation of **10a**, treatment of 3-nitropropanol **12**[8] (0.25 g, 2.21 mmol) with pyridine (2.5 mL) and acetic anhydride (2.5 mL) led to the title compound as a colorless oil (0.28 g, 93%): R_f 0.70 (1:1 hexane/ethyl acetate); ν_{max} (film) (cm^{-1}) 2992 (C–H), 1740 (C=O), 1557, 1385 (NO_2), 1240 (C–O); ^1H NMR ($CDCl_3$) δ 4.47 (t, 2H, $J_{2,3}$=6.7 Hz, H-3, H-3′), 4.17 (t, 2H, $J_{1,2}$=6.0 Hz, H-1, H-1′), 2.34 (m, 2H, H-2, H-2′), 2.04 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 170.6 (O*C*OCH$_3$), 72.2 (C-3), 60.6 (C-1), 26.3 (C-2). CI MS *m/z* (rel. int.): 148 (M+H, 19), 130 (M+H−H_2O, 8), 115 (M+H−H_2O−CH_3, 45), 101 (M−NO_2, 53), 88 (M+H–HOAc, 100). HRMS (CI) calcd for $C_5H_9NO_4$+H: 148.0609. Found $(M+H)^+$ 148.0584.

3.1.10. Sodium salt of 3-nitropropanol (14). *Method A*. To a stirred solution of 3-nitropropanol **12**[8] (1.00 g, 9.51 mmol) in methanol (14 mL) was added dropwise 2 M sodium methoxide in methanol (5.91 mL, 11.80 mmol). After 5 h at room temperature, the reaction mixture was treated with activated charcoal, filtered and the solvent evaporated, thus affording 1.07 g (quantitative yield) of compound **14** as a crude white solid, which was washed with cold acetone: R_f 0.40 (10:1 ethyl acetate/ethanol); ν_{max} (KBr) (cm^{-1}) 3000–3500 (OH), 2900–2800 (C–H), 1700, 1638 (C=N); ^1H NMR (D_2O) δ 6.20 (t, 1H, $J_{2,3}$=6.2 Hz, H-3), 3.72 (t, 2H, $J_{1,2}$=6.4 Hz, H-1, H-1′), 2.50 (m, 2H, H-2, H-2′); ^{13}C NMR (D_2O) δ 117.1 (C-3), 59.2 (C-1), 30.8 (C-2).

Method B. Treatment of 3-acetoxy-1-nitropropane **13** as described above for **12** yielded quantitatively the salt **14**.

3.1.11. 3-Acetoxy-1-nitropropane (13), 3-acetoxy-(*N*-acetyl-*N*-acetoxy)-propionamide (15) and 2,3-diacetoxypropanenitrile (16). Following the same procedure above described for the preparation of **10a**, treatment of the sodium salt of 3-nitropropanol **14** (0.97 g, 7.63 mmol) with pyridine (10 mL) and acetic anhydride (10 mL), led to a crude oily residue (1.15 g), whose ^1H NMR spectrum showed it contained, almost exclusively, a mixture of the title compounds **13**, **15** and **16** in a relative ratio 1.6:2.2:1, respectively. Preparative thin layer chromatography of this mixture (1:1 hexane/ethyl acetate) afforded a fraction with pure **15**, whereas both **13** and **16** remain inseparable; thus spectral data for **16** were obtained after subtracting the spectra of **13** from the spectra of mixture **13**+**16**. *Data for **15***. Colorless oil; R_f 0.60 (1:1 hexane/ethyl acetate); ν_{max} (film) (cm^{-1}) 1734 (C=O), 1557, 1368 (NO_2), 1240, 1042 (C–O); ^1H NMR ($CDCl_3$) δ 4.40 (t, 2H, $J_{2,3}$=6.2 Hz, H-3, H-3′), 3.10 (m, 1H, H-2), 3.00 (m, 1H, H-2′), 2.38 (br s, 3H, NAc), 2.33 (s, 3H, NOAc), 2.06 (br s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 170.7 (O*C*OCH$_3$), 167.6 (C-1, N*C*OCH$_3$), 167.2 (NO*C*OCH$_3$), 58.6 (C-3), 35.5 (C-2), 24.0 (NOCO*C*H$_3$), 20.7 (OCO*C*H$_3$), 17.8 (NCO*C*H$_3$). CI MS *m/z* (rel. int.): 232 (M+H, 90), 190 (M+H−C_2H_2O, 81), 172 (M+H–HOAc, 77), 130 (M+H–HOAc−C_2H_2O, 43), 115 (M−$C_4H_6NO_3$, 100). HRMS

(CI) calcd for $C_9H_{13}NO_6$+H: 232.0811. Found $(M+H)^+$ 232.0810. *Data for* ***16***. R_f 0.70 (1:1 hexane/ethyl acetate); ν_{max} (film) (cm^{-1}) 2327 (CN); ^1H NMR ($CDCl_3$) δ 5.58 (t, 1H, $J_{2,3}$=4.5 Hz, $J_{2,3'}$=5.7 Hz, H-2), 4.69 (dd, 1H, $J_{3,3'}$= 12.0 Hz, H-3), 4.36 (dd, 1H, H-3′); ^{13}C NMR ($CDCl_3$) δ 170.6, 169.7 ($OCOCH_3$), 117.7 (CN), 61.6 (C-3), 59.1 (C-2), 20.3 ($OCOCH_3$). CI MS *m/z* (rel. int.): 172 (M+H, 4), 130 (M+H–C_2H_2O, 6), 112 (M+H–HOAc, 100), 88 (M+H–C_2H_2O–C_2H_2, 51). HRMS (CI) calcd for $C_7H_9NO_4$+H: 172.0609. Found $(M+H)^+$ 172.0604.

3.1.12. *N*-Acetoxy-2,3,5,6,7-penta-*O*-acetyl-D-*glycero*-L-*manno*-1,4-lactone oxime (24a), (*E*)-3,4,5,6,7-penta-*O*-acetyl-1-nitro-D-*galacto*-hept-1-ene (25a) and *N*-acetoxy-2,3,5,6,7-penta-*O*-acetyl-D-*glycero*-L-*manno*-1,5-lactone oxime (27a). To a stirred solution of 1-deoxy-1-nitro-D-*glycero*-L-*manno*-heptitol **23a**[13] (1.00 g, 4.15 mmol) in 2 M NaOH (10 mL) was added cold methanol (40 mL). After several minutes at 0°C, there was apparition of a white precipitate and the reaction mixture was kept in the refrigerator for 24 h; then, the resulting hygroscopic solid was filtered, washed on the filter with cold methanol and dried in a vacuum dessicator (1.09 g). Subsequently, this solid was treated with pyridine (4 mL) and acetic anhydride (8 mL) as described for **10a**, thus affording a crude oily residue (1.37 g), whose ^1H NMR spectrum showed it contained, almost exclusively, a mixture of **24a**, **27a**, and known **25a**,[13] in a relative ratio 3.6:1.0:2.6, respectively. Analytically pure samples of these three products could be isolated by preparative thin layer chromatography (1:1 hexane/ethyl acetate). *Data for* ***24a***. Colorless oil; R_f 0.22 (1:1 hexane/ethyl acetate); $[\alpha]_D$=+8.0°, $[\alpha]_{578}$=+7.3°, $[\alpha]_{546}$=+8.9°, $[\alpha]_{436}$=+18.0°, $[\alpha]_{365}$=+28.9° (*c* 0.80, $CHCl_3$); ν_{max} (film) (cm^{-1}) 2954 (C–H), 1755 (C=O), 1694 (C=N), 1260, 1036 (C–O); ^1H NMR ($CDCl_3$) δ 5.97 (d, 1H, $J_{2,3}$=4.5 Hz, H-2), 5.69 (dd, 1H, $J_{3,4}$=2.9 Hz, H-3), 5.54 (dd, 1H, $J_{4,5}$=9.5 Hz, $J_{5,6}$=2.6 Hz, H-5), 5.49 (ddd, 1H, H-6), 4.65 (dd, 1H, H-4), 4.32 (dd, 1H, $J_{6,7}$= 5.4 Hz, $J_{7,7'}$=11.7 Hz, H-7), 4.01 (dd, 1H, $J_{6,7'}$=6.5 Hz, H-7′), 2.16 (s, 3H, OAc), 2.13 (s, 3H, OAc), 2.10 (s, 6H, 2OAc), 2.05 (s, 6H, 2OAc); ^{13}C NMR ($CDCl_3$) δ 170.3, 169.5, 169.4, 169.1 ($OCOCH_3$), 167.6 ($NOCOCH_3$), 158.0 (C-1), 78.9 (C-4), 68.7, 68.6, 66.4 (C-2, C-3, C-5, C-6), 61.5 (C-7), 20.6, 20.3, 19.1 ($OCOCH_3$ and $NOCOCH_3$). CI MS *m/z* (rel. int.): 476 (M+H, 100), 434 (M−C_2H_3N, 32), 415 (M−HOAc, 15), 392 (M−C_2H_3N–C_2H_2O, 7), 374 (M−HOAc–C_2H_3N, 11), 331 (M−HOAc–C_2H_3N–$COCH_3$, 15), 314 (M−2HOAc–C_2H_3N, 5). HRMS (CI) calcd for $C_{19}H_{25}O_{13}N$+H: 476.1404. Found $(M+H)^+$ 476.1395. *Data for* ***27a***. Colorless oil; R_f 0.12 (1:1 hexane/ethyl acetate); $[\alpha]_{578}$=−0.8°, $[\alpha]_{546}$=−1.6°, $[\alpha]_{436}$=−4.0° (*c* 0.50, $CHCl_3$); ν_{max} (film) (cm^{-1}) 2959 (C–H), 1748 (C=O), 1661 (C=N), 1223, 1040 (C–O); ^1H NMR ($CDCl_3$) δ 6.01 (d, 1H, $J_{2,3}$=3.6 Hz, H-2), 5.43 (dd, 1H, $J_{4,5}$=9.5 Hz, $J_{3,4}$=8.3 Hz, H-4), 5.33 (ddd, 1H, H-6), 5.29 (dd, 1H, H-3), 4.46 (dd, 1H, $J_{6,7}$=6.0 Hz, $J_{7,7'}$=11.5 Hz, H-7), 4.30 (dd, 1H, $J_{5,6}$=2.7 Hz, H-5) 4.41 (dd, 1H, $J_{6,7'}$=7.0 Hz, H-7′), 2.16 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.02 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 170.3, 169.8, 169.4, 169.1, 168.8, 167.4 ($OCOCH_3$ and $NOCOCH_3$), 154.2 (C-1), 69.5, 66.8, 65.2, 64.3 (C-2, C-3, C-4, C-5, C-6), 61.2 (C-7), 20.7, 20.6, 20.5, 19.3 ($OCOCH_3$ and $NOCOCH_3$).

3.1.13. *N*-Acetoxy-2,3,5,6,7-penta-*O*-acetyl-D-*glycero*-D-*galacto*-1,4-lactone oxime (24b), (*E*)-3,4,5,6,7-penta-*O*-acetyl-1-nitro-D-*manno*-hept-1-ene (25b) and 2,3,4,5,6,7-hexa-*O*-acetyl-D-*glycero*-D-*galacto*-heptononitrile oxide (26b). Following the procedure described in Section 3.1.12, 1-deoxy-1-nitro-D-*glycero*-D-*galacto*-heptitol **23b**[14] (1.00 g, 4.15 mmol) led to an oily residue (1.25 g), whose ^1H NMR spectrum showed that it contained a mixture of **24b**, **26b**, and known **25b**[14] (4.5:1.0:3.5 respective ratio), together with other minor unidentified products. Analytically pure samples of these three products could be isolated by preparative thin layer chromatography (1:1 hexane/ethyl acetate). *Data for* ***24b***. Colorless oil; R_f 0.24 (1:1 hexane/ethyl acetate); $[\alpha]_D$=+40.7°, $[\alpha]_{578}$=+43.4°, $[\alpha]_{546}$= +49.1°, $[\alpha]_{436}$=+86.3° (*c* 0.7, $CHCl_3$); ν_{max} (film) (cm^{-1}) 2954 (C-H), 1746 (C=O), 1688 (C=N), 1215, 1047 (C–O); ^1H NMR ($CDCl_3$) δ 5.84 (d, 1H, $J_{2,3}$=2.9 Hz, H-2), 5.51 (dd, 1H, $J_{4,5}$=3.8 Hz, $J_{5,6}$=6.4 Hz, H-5), 5.28 (m, 1H, H-6), 5.19 (t, 1H, $J_{3,4}$=3.2 Hz, H-3), 4.66 (t, 1H, H-4), 4.41 (dd, 1H, $J_{7,7'}$=12.6 Hz, $J_{6,7}$=2.9 Hz, H-7), 4.22 (dd, 1H, $J_{6,7'}$=5.4 Hz, H-7′), 2.18 (s, 3H, OAc), 2.16 (s, 3H, OAc), 2.14 (s, 3H, OAc), 2.13 (s, 3H, OAc), 2.11 (s, 3H, OAc), 2.07 (s, 3H, OAc); ^{13}C NMR ($CDCl_3$) δ 170.7, 169.9, 169.7, 169.2, 167.8 ($OCOCH_3$), 159.6 (C-1), 85.1 (C-4), 75.4, 73.0, 69.9, 68.8 (C-2, C-3, C-5, C-6), 61.4 (C-7), 21.0, 20.9, 20.7, 19.3 ($OCOCH_3$ and $NOCOCH_3$). CI MS *m/z* (rel. int.): 476 (M+H, 75), 433 (M−C_2H_2O, 79), 416 (M−OAc, 14), 392 (M−C_2H_2O–C_2H_2N, 7), 374 (M−OAc–C_2H_2O, 19), 373 (M−C_2H_2O–HOAc, 33), 332 (M−2C_2H_2O–C_2H_2N–HOAc, 19), 314 (M−OAc–C_2H_2O–HOAc, 13), 290 (M−2C_2H_2O–C_2H_2N–HOAc, 19), 254 (M−OAc–C_2H_2O–2HOAc, 25), 211 (M−OAc–C_2H_2O–2HOAc–NHCO, 50), 169 (M−OAc–2C_2H_2O–2HOAc–NHCO, 100). HRMS (CI) calcd for $C_{19}H_{25}O_{13}N$+H: 476.1404. Found $(M+H)^+$ 476.1385. *Data for* ***26b***. Colorless oil; R_f 0.15 (1:1 hexane/ethyl acetate); ν_{max} (film) (cm^{-1}) 2940 (C–H), 2350 (C≡N), 1753 (C=O), 1227, 1044 (C–O); ^1H NMR ($CDCl_3$) δ 5.54 (dd, 1H, $J_{2,3}$= 1.0 Hz, $J_{3,4}$=11.7 Hz, H-3), 5.47 (dd, 1H, $J_{4,5}$=1.3 Hz, H-4), 5.35 (d, 1H, $J_{5,6}$=8.9 Hz, H-5), 5.20 (d, 1H, H-2), 5.05 (m, 1H, H-6), 4.21 (dd, 1H, $J_{6,7}$=2.6 Hz, $J_{7,7'}$= 12.5 Hz, H-7), 4.01 (dd, 1H, $J_{6,7'}$=5.4 Hz, H-7′), 2.19 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.04 (s, 3H, OAc). ^{13}C NMR ($CDCl_3$) δ 170.5, 170.1, 170.0, 169.8, 169.4, 168.9 ($OCOCH_3$), 67.9, 67.3, 67.0, 66.9, 66.7 (C-2, C-3, C-4, C-5, C-6), 61.9 (C-7), 20.8, 20.6, 20.5, 20.3, 18.2 ($OCOCH_3$). CI MS *m/z* (rel. int.): 476 (M+H, 44), 433 (M−C_2H_2O, 67), 416 (M−OAc, 13), 374 (M−OAc–C_2H_2O, 8), 359 (M−C_2H_2O–CH_3CO–NOH, 100), 331 (M−OAc–C_2H_2O–CH_3CO, 15), 328 (M−2HOAc–NOH, 28), 314 (M−C_2H_2O–AcOH–OAc, 8). HRMS (CI) calcd for $C_{19}H_{25}O_{13}N$+H: 476.1404. Found $(M+H)^+$ 476.1424.

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18. A similar attack of HO-5 on C-1 of the hypothetic acetic nitronic anhydride from **23a** would explain the formation of the 1,5-lactone oxime **27a**.